

REMARKS

Claims 27-44 are pending in the present application. By this Amendment, claim 27 is amended to replace "comprising" with "consisting essentially of." No new matter has been added. Entry of the amendment is respectfully requested.

Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks. For the Examiner's convenience, Applicant's remarks are presented in the order in which they were raised in the Office Action.

A. Insertion of "SEQ ID NOs" in the Specification

The Examiner requires the entry of SEQ ID NOs in the Specification in accordance with 37 C.F.R. §1.821. Applicants note that amendments to the Specification introducing sequence identifiers were submitted by a Preliminary Amendment filed on February 19, 2002. A courtesy copy of the Preliminary Amendment is enclosed herewith for the Examiner's convenience.

B. Declaration of Amy J. Weiner under 37 C.F.R. § 1.132

In support of their arguments below, Applicants submit a declaration under 37 C.F.R. §1.132 from Amy J. Weiner, Ph.D. which provides statements of fact showing that the specification provides an adequate *written description* of the claimed invention to one of skill in the art and the claimed HCV NS3 protease is not indefinite. A copy of the declaration originally submitted in the reexamination (U.S. Ser. No. 10/438,313) of the parent case (U.S. Patent No. 5,371,017) is provided. The instant application is in a CON/DIV chain of U.S. Patent No. 5,371,017 and has the same specification.

Applicants note that the 37 C.F.R. §1.132 declaration from Amy J. Weiner, Ph.D. submitted in the parent case (executed copy submitted) refers to the specification of the published 5,371,017 patent in terms of column and line numbers. For the Examiner's convenience Applicants are also providing a chart of column and line numbers of the '017 patent cited in the declaration referring to the corresponding page and line numbers of the instant specification. An unexecuted version of the declaration incorporating the page/line numbers for the instant application is also provided.

C. Claim Rejections Under 35 U.S.C. § 101

Claims 27-31 remain rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the Examiner asserts that the claimed composition comprises a polynucleotide that is indistinguishable from the HCV genome.

In response, Applicants amend claim 27 to specify that the claimed composition comprises "an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide, wherein said polypeptide consists essentially of an HCV NS3 domain protease." (emphasis added). Applicants submit that the claimed isolated polynucleotide, as amended, does not read on the native HCV genome.

Therefore, Applicants respectfully request withdrawal of this ground for rejection.

D. Double Patenting

Claims 27-43 remain rejected, and claim 44 is newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017.

Claim 36 remains provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017.

Applicants submit that they will file a terminal disclaimer in the present application to disclaim any term beyond the term of any earlier expiring patent in order to overcome this ground for rejection, after the conflicting claims are found to be allowable.

E. Claim Rejections under 35 U.S.C. §112

(i) Claims 27-44 are rejected under 35 U.S.C. § 112, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically the Examiner states that the expression constructs of the specification while being necessary for HCV protease activity have been shown to be insufficient. In particular, the Examiner states that the functional description of an HCV NS3 protease exemplified by

Examples 4 and 5 and the descriptions of NS3 domain by analogy with flaviviruses are insufficient.

The Examiner questions the truncation experiments of Example 5 with bacterially expressed hSOD fusions, which indicate that P600, P500 and P300 constructs (with progressive C terminal truncations) display a specific protease cleavage product whereas the P190 construct (with the largest C-terminal deletion) does not display such activity, thus demonstrating HCV NS3 domain specific protease activity.

The Examiner hypothesizes that the hSOD-HCV fusion proteins may have resulted in inclusion bodies. However, the Examiner fails to provide any reason why only the P190 construct produces inclusion bodies while the other larger constructs remain available for proteolytic cleavage if, as the Examiner alleges, the production of the 34kDa proteolysis product is indeed due to bacterial (non-HCV) proteases.

(a) An HCV protease activity is disclosed in the specification.

Applicants respectfully traverse and submit that a Written Description of " HCV NS3 domain protease" is provided in the specification. An HCV protease encoded by the NS3 domain in at least one strain of HCV is further described with reference to a 202 amino acid protease sequence from SEQ ID NO: 1 in page 6, line 22 to page 7, line 18 (*see* SEQ ID NO: 65); the corresponding polynucleotide sequence is disclosed in Figure 1. HCV protease activity associated with a 299 amino acid HCV polypeptide encoded by SEQ ID NOS: 66 and 68 and specified in claims 6 and 14 are described in Example 5. HCV protease activity associated with a 686 amino acid HCV polypeptide shown in Figure 1 and encoded by SEQ ID NO: 70, and specified in claim 2 is described in Examples 4 and 5.

Whether a patent specification adequately describes the subject matter claimed is a question of fact. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). In support of their arguments below, Applicants submit a declaration under 37 C.F.R. §1.132 from Amy J. Weiner, Ph.D. which provides statements of fact showing that the specification provides an adequate *written description* of the claimed invention to one of skill in the art. ("If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing ... then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578,

1584 (Fed. Cir. 1996)). Statements of fact presented in a 1.132 declaration may not be dismissed "without an adequate explanation of why the declaration failed to rebut the Board's prima facie case of inadequate description." (*Id.* 76 F.3d 1168, at 1174).

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing Examples 4 and 5 of the specification that a HCV NS3 protease activity associated with a specific segment of HCV polyprotein is disclosed in the specification. (*see* Decl. of Amy J. Weiner, ¶¶ 5-14.)

(b) A peptide substrate for the HCV protease is provided in the specification

Applicants submit that a peptide substrate for a HCV protease is also disclosed in the specification. The protease activity described in Examples 5 (A), (B), and (C) was observed through self-cleavage of a hSOD-HCV fusion protein wherein the HCV peptide portion corresponded to amino acids 1-686 of Fig. 1 and various truncations thereof. Observance of specific cleavage within the NS3 region of HCV is described in every instance where protease activity was observed. For example, "34 kDa band correspond[ing] to the hSOD partner (about 20 kDa) with a portion of the NS3 domain" was observed in each case with the P600, P300 and P500 fusion proteins of NS3 fused to a hSOD leader, but not with the inactive P190 fusion protein.

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing Examples 4 and 5 of the specification that a peptide substrate for a HCV protease activity is disclosed in the specification. (*see* Decl. of Amy J. Weiner, ¶ 15.)

(c) Subsequent research confirms that the protease activity observed in Example 5 is caused by a specific HCV NS2/3 protease encoded within the sequence of Fig. 1

Applicants respectfully traverse the Examiner's position that the protease activity shown in Examples 4 and 5 cannot be attributed to activities of the art-recognized NS3 domain encoded proteases, NS3 serine protease and NS2/3 protease.

As noted by the Examiner, a serine protease encoded in the N-terminal region of the NS3 domain is responsible for cleavage of the HCV polyprotein at sites downstream of the NS3 gene. The NS2 protein extends from amino acid 810 to amino acid 1026, and cleavage at the NS2-NS3 junction involves a second viral protease which comprises part of the NS2 region and the entire NS3 domain. The Examiner alleges that while the Specification discloses structures

corresponding to the NS3 serine protease (e.g., SEQ ID NO:65) it does not disclose structures corresponding to the NS2/3 protease (page 9 of the Office Action). Applicants respectfully traverse and state that the experiments described in Example 5 correspond to the NS2/3 protease activity for the following reasons:

- The fusion proteins expressed in Example 5, comprise 1-151 amino acids from hSOD (human superoxide dismutase gene) and amino acids 946-1630 of HCV (corresponding to amino acids 1-686 of Figure 1) and C-terminal truncations therefrom. *See* col. 18, lines 19-22.¹
- The putative cleavage site for the NS2/3 protease is between Leu-1026 and Ala-1027. (Grakoui, PNAS 1993, p. 10584). These residues correspond to amino acids 81 and 82 of the sequence of Figure 1. Fused with a 151 amino acid hSOD leader peptide, these are expected to produce a fragment of about 232 amino acids upon NS2/3 cleavage. In Example 5 of the specification, P600, P500 and P300 fusion proteins resulted in the observation of a proteolytic fragment estimated by gel electrophoresis to migrate at 34 kDa corresponding to about 20kDa of hSOD and some HCV sequences. P190 which is inactive, does not produce a 34 kDa product but only a full length 40kDa protein corresponding to a theoretically uncleaved product. The proteolytic fragments were identified by anti-HCV sera indicating that only fusion proteins containing HCV sequences were observed.
- Subsequent characterization of the NS2/3 protease has shown it to be a cysteine protease and site-directed mutagenesis studies have identified His-952 and Cys-993, numbered according to their location within the HCV polyprotein, as essential for its activity. (Pallaoro et al. J. Virol. 9939-9946 (2001); Hijikata et al. J. Virol 67(8):4665-4675 (1993); Grakoui et al. PNAS 90:10583-10587 (1993)). His-952 corresponds to amino acid 7 of Figure 1 and Cys-993 corresponds to amino acid 48 of the sequence of Fig. 1. Thus the amino acid residues corresponding to the two

¹ Example 4 reports how the clones used in Example 5 were constructed. The largest construct used was p600. According to Example 4, this construct encompassed amino acids 946-1630 of HCV. Grakoui (PNAS 1993) reported that NS3 consists of amino acids 1027-1657 of HCV. A comparison of the HCV amino acids included in p600 with the NS3/NS4 boundaries reported in Grakoui discloses that the downstream ends of the Example 5 constructs stop short of the NS3/NS4 boundary, which occurs after amino acid 1657, while their upstream ends included what is now understood to be a portion of NS2.

residues essential for NS2/3 protease activity are within the sequence of Figure 1 and the constructs of Example 5.

- The NS 2/3 viral protease includes most of the NS2 region and the entire NS3 serine protease domain, amino acids 849 to 1237. The catalytic activity of the serine protease is not required for the NS2–NS3 cleavage (Hijikata et al. J. Virol 67(8):4665-4675 (1993); Grakoui et al. PNAS 90:10583-10587 (1993)).² However, the NS3 portion of the viral enzyme cannot be substituted by other fragments of the HCV polypeptide. (Santolini et al. J. Virol. 69:7461–7471. (1995)). Santolini shows that while a NS2-NS3 polypeptide extending to HCV residue 1237 is active for NS2/3 protease activity, a polypeptide extending to residue 1137 is not. (*see* Fig. 1B of Santolini). The results of Example 5 shows that fusion protein P190 extending to amino acid 1145 is inactive while fusion protein P300 extending to amino acid 1245 is active. Thus Example 5 corresponds to the observations of Santolini about the requirement for the minimum length of NS3 sequence for NS2/3 protease activity.
- The Examiner relies on Pallaoro and Thiebault for alleging that 113 C-terminal amino acids of NS2 are critical for NS 2/3 protease activity. (p. 11 of the Office Action). Applicants respectfully disagree. First, no reference cited by the Examiner identifies that any specific residue upstream of His-952 and Cys-993 is necessary for activity. Second, the experiments in these references and others (e.g., Hijikata, Grakoui and Santolini) are fundamentally different from Example 5, as they use *in vitro* translated proteins that do not have (or have fewer than 10) amino acids upstream of the N-terminal NS2 truncation fragment. In contrast to the lack of (or very few) amino acids in the upstream sequences, a 151 amino acid hSOD leader peptide is attached to the N-terminus of the fusion proteins expressed in Example 5. The Examiner admits that the active site residues are within the NS3 region and 79 C-terminal amino acids of the NS2 region are present in each and every fusion construct (page 10 of the Office Action). Therefore, it is likely that the observed HCV sequence specific cleavage of the hSOD fusions was due to NS2/3 protease where the presence of upstream hSOD

² Hijikata states "[t]he catalytic activities of these two proteinases are separable, because some mutants, such as S1165A and H952A, retained only one of these activities. However, the regions required for detection of these activities in the HCV precursor polyprotein overlapped." (p. 4673). Applicants further note that the experiments of

amino acids were able to generate NS2/3 protease activity. This explanation is entirely consistent with the results observed in Example 5.

- The NS 2/3 cleavage activity is affected by microsomal membranes (Santolini) and detergents (Pieroni). Activity is inhibited by mutations that perturb local conformation and suggest the importance of correct folding of the NS 2/3 polypeptide for proper cleavage activity. (Pieroni, at 6373; *see also* Hijikata; Grakoui (PNAS, 1993); Reed et al. J. Virol. 69:4127-4136 (1995)). The NS2 protein extends from HCV residue 810, and the NS2/3 protease extends between HCV residues 810 and 1206 (*Id.*). However, various groups have been able to delete numerous residues upstream of His-952 and Cys-993 and retain activity. Thibeault *et al.* have been able to express the NS2/3 protease in bacteria and observed significant protease activity in NS2/3 peptides extending from residue 904 and lesser but detectable activity in peptides containing residues 915-1206. (*see* Fig. 2C in J. Biol. Chem. 276(49):46678-46684 (2001).) Thibeault's expression system only adds 10 upstream amino acids (*Id.* at p. 46679).

Applicants submit that there is no demonstrated requirement for specific residues at specific positions upstream of His-952 and Cys-993. As few as about 40 upstream residues demonstrate significant activity (Thibeault). Thus, the fusion of a 151 amino acid fragment from hSOD to the 946-1630 HCV fragment was sufficient to generate NS2/3 protease activity in the fusion proteins of Example 4 as evidenced by the results of Example 5.

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing the specification and the literature that the HCV protease activity disclosed in the specification is attributable to NS2/3 protease. (*see* Decl. of Amy J. Weiner, ¶¶ 22-34.) Therefore, Applicants respectfully submit that the results of Example 5 disclose a NS2/3 protease activity associated with the NS3 domain of HCV as described in Figure 1.

(d) A constructive reduction to practice of the NS2/3 protease is described in the specification

Applicants submit that the specification provides prophetic description of protease assays designed to show HCV protease activity associated with the HCV NS3 domain. Example 10 of

Cindy Lee referred to by the Examiner and the Eckart paper discussed below confirm that mutation of the serine-

the specification discloses the use of a pGEM-3Z/Yellow Fever Leader vector for in vitro expression of HCV protease. In vitro transcription and translation of the clone HCV protease using transcription and translation systems from Promega are disclosed in Example 11, column 23 of the specification.

These experiments were subsequently carried out and results reported by Eckart et al. in Biochem. Biophys. Res. Commun. 192:399-406 (1993). Expression in a rabbit reticulocyte system of a pGEM-3YPN vector containing 5' truncated NS2 and 3' truncated NS3 fragment of HCV (corresponding to HCV amino acids 840-1619)³ showed protease activity encoded by this region. (Eckart p. 403 and Fig. 2). When the NS2'-NS3' fragment was tested with a mutation at Ser-1165, Eckart found that "[i]dentical polypeptide profiles [of the protease products] were observed in translation of both wild type and mutant RNA templates (Fig. 2) indicating that the NS2/NS3 cleavage occurs inefficiently but independently of Ser₁₁₆₅." (Eckart, p. 403).

The Eckart paper confirms the Specification's prophetic example of a protease encoded by the 5' truncated NS2 and 3' truncated NS3 fragment of HCV. Since these experiments were conducted in a mammalian rabbit reticulocyte system, the Examiner's concern that the protease activity is possibly "bacterial" cannot be sustained.

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing the specification that the HCV protease activity disclosed in the specification could not be bacterial. (see Decl. of Amy J. Weiner, ¶¶ 16-21.)

(e) The structure of a protease consisting of the amino acid sequence of SEQ ID NO:65 is described in the specification

Applicants submit that the Example 5 experiments are directed to upstream cleavage encoded by NS 2/3 protease and are not provided to demonstrate the NS3 serine protease activity which is also encompassed within the NS3 domain shown in Fig. 1.

In the Specification, a 202 amino acid sequence corresponding to SEQ ID NO: 65 is disclosed as substantially encoding a HCV protease. Table 1 discloses HCV peptides from within SEQ ID NO: 65 and by alignment with catalytic residues of flavivirus serine proteases, identifies His-1083 and Ser-1165 of the HCV genome as active residues for serine protease activity.

1165 residue which inactivates NS3 serine protease, does not affect the activity of the NS2/3 protease.

Examples 10 and 11 provide methods for expression *in vitro* of HCV protease as a method for confirming the disclosure of HCV NS3 serine protease.

The invention was subsequently reduced to actual practice and published by a group of authors including the inventors of the instant patent. Eckart *et al.* used an *in vitro* transcription translation system to demonstrate a protease activity encoded by the NS3 domain that was mediated by the Ser-1165 residue identified in Table 1 of the specification. (Biochem. Biophys. Res. Commun. 192:399-406 (1993).)

The Specification discloses the structure of an HCV NS3 domain and describes a function (HCV protease) attributed to the structure. Therefore Applicants traverse the Examiner's contention that the disclosure is insufficient. By disclosing in a patent application a structure that inherently has a property, a patent application necessarily discloses that function. *In re Reynolds*, 443 F.2d 384, 170 U.S.P.Q. 94 (CCPA 1971). Subsequent disclosure of an inherent property of a product disclosed in an earlier application does not bar that product from obtaining benefit of the earlier filing date. *Kennecott Corp. v. Kyocera Internat'l*, 835 F.2d 1419, 1423. (Fed. Cir. 1987). Since, the specification describes the structure of HCV NS3 protease, and the structure is subsequently found to inherently possess the function (protease) specified in the pending claims, Applicants submit that written description of the claims is satisfied.

The specification provides a general description of suggested utility for a HCV protease that links the HCV protease function with self-cleavage activity and suggests a method for assaying expression and activity based on this auto-catalytic activity. Applicants submit that the SEQ ID NOS: 1, 65, 66, 68 or 70 proteases are not claimed as a substrate for protease activity but solely as a protease itself. The utility described in the specification can still be met by using a full-length HCV polyprotein as a substrate and the SEQ ID NOS: 1, 65, 66, 68 or 70 proteases as the enzyme.

The Examiner states that the proteases corresponding to SEQ ID NOS: 1, 65, 66, 68 or 70 only contain the NS2/3 cleavage site which is a substrate of the NS2/3 "protease" and not the NS3 serine protease. Applicants submit that their claims specify "a hepatitis C virus (HCV) NS3 domain protease," which does not imply any particular protease. Actual reductions to practice of

³ The Eckart fragment expressed in the rabbit reticulocyte system corresponds to HCV amino acids 840-1619, while the cf1SODp600 corresponds to amino acids 946-1630 of HCV.

NS2/3 protease activity associated with SEQ ID NOS: 1, 65, 66, 68 or 70 proteases using p300, p500 and p600 as substrates are shown in Example 5 of the specification as discussed above.⁴

SEQ ID NO: 65 relates to a serine protease structure as its sequence does not include amino acid residues essential for NS2/3 activity. The NS4A cofactor referred by the Examiner relates to the activity of a serine protease encoded by the NS3 region at particular sites of a particular substrate. The Examiner states that for efficient cleavage at all of the natural cleavage sites an additional HCV peptide (NS4A) is needed.

In fact, NS4A is not essential for the activity of a hepatitis C virus NS3 serine protease ("while NS4A appears to be absolutely required for *trans*-cleavage at the 4B/5A site, it is not an essential cofactor for serine protease activity." (see Abstract, lines 10-11, page 8151 right column (first full paragraph) of Lin *et al.*, J. Virol. 68(12): 8147-8157 (1994)). Further *cis*-cleavage by NS3 domain proteases does not require NS4A. (Lin *et al.* p. 8149, right col.; p. 8152, right col.; Fig. 7A; p. 8155, left col.).⁵

The SEQ ID NO:65 protein is identified as a serine protease and constructively reduced to practice.⁶ Therefore, Applicants submit that SEQ ID NO:65 discloses a functional serine protease as identified in the Specification by alignment and homology and constructively reduced to practice in Examples 10 and 11 (pages 37-39), as discussed in the previous section. The NS3 serine protease is active as a protease by itself – independently active on some substrates and weakly active in the absence of NS4A on other substrates.

In summary, Applicants respectfully traverse the Examiner's position that the specification needs to describe individual structures of a NS3 serine protease and a NS2/3 protease. These specific protease activities are not specified in the claims. Applicants submit that

⁴ SEQ ID NO:65 (and SEQ ID NO: 1) consists of residues 1005-1204 of the HCV polyprotein. Eckart *et al.* (Biochem Biophys Res Commun. 1993 Apr 30;192(2):399-406; Ref. 427) shows that the serine protease catalytic site is dependent on Ser¹¹⁶⁵ which is encompassed within the SEQ ID NOS: 1, 65, 66, 68 and 70 proteases.

⁵ The abstract of Lin *et al.* states that the cleavage at NS3/4A, NS4A-4B and NS5A-5B are processed efficiently in *trans* by the NS3 serine protease without NS4A as follows:

By using an NS3-5B substrate with an inactivated serine proteinase domain, *trans*-cleavage was observed at all sites except for the 3/4A site. Deletion of the inactive proteinase domain led to efficient *trans*-processing at the 3/4A site. Smaller NS4A-4B and NS5A-5B substrates were processed efficiently in *trans*; however, cleavage of an NS4B-5A substrate occurred only when the serine proteinase domain was coexpressed with NS4A.

Abstract, Lin *et al.*, J. Virol. 68(12): 8147-8157 (1994).

the specification describes at least one protease activity specifically associated with the NS3 region and provides disclosure of a substrate for such protease activity. Thus one of skill in the art would have identified the NS3 domain described in the Specification and understood that at the time of filing of the application, the inventors had possession of the claimed invention. Therefore, applicants respectfully request withdrawal of this ground for rejection for lack of written description under 35 U.S.C. § 112, first paragraph.

If the rejection is maintained, Applicants request the Examiner to provide an affidavit under 37 C.F.R. 1.104(d)(2) stating facts within the knowledge of the Examiner as to why the rejection should be maintained. Applicants reserve to right to explain or contradict the assertion with their own affidavits.

(ii) Claims 29, 30, 34, 35, 39 and 40 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 29, 30, 34, 35, 39 and 40 specify SEQ ID NOS; 63 and 64 of the art-accepted histidine and serine respectively of the catalytic triad of the HCV NS3 serine protease. (Footnote 9 on page 12 of the Office Action). As discussed above, the structure of a serine protease is described in the specification and constructive reduction to practice of serine protease activity is also disclosed. Applicants submit that the structural features of a serine protease comprising the catalytic triad residues is disclosed in the specification and respectfully request withdrawal of this ground for rejection.

If the rejection is maintained, Applicants request the Examiner to provide an affidavit under 37 C.F.R. 1.104(d)(2) stating facts within the knowledge of the Examiner as to why the rejection should be maintained. Applicants reserve to right to explain or contradict the assertion with their own affidavits.

(iii) Claims 27-44 are rejected under 35 U.S.C. § 112, first paragraph

The Examiner asserts that Specification does not reasonably provide enablement for the preparation of a composition comprising a protease encoded by any of the P600, P500, P300 or

⁶ The Examiner notes (page 10) that SEQ ID NO:65 consists of residues 1005-1204 of the HCV polyprotein. Eckart *et al.* (Biochem Biophys Res Commun. 1993 Apr 30;192(2):399-406; Ref. 427) shows that the serine protease

P190 constructs or comprising more than the HCV amino acid sequence region present in SEQ ID NO:68, or a generic version thereof, or an active truncation analog thereof, or an assay conducted with such a protease. The specification is further alleged to not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner asserts that the specification does not describe any polynucleotides encoding a protease capable of cleaving either NS2/3 and NS3/4 junctions. Applicants respectfully traverse. As discussed in detail *supra*, the structure and activity of a NS2/3 protease is disclosed in Examples 4 and 5.

Further, the structure of a NS3 serine protease is described along with a constructive reduction to practice. As also noted above, the serine protease is active at certain sites in the absence of NS4A cofactor and such substrates (whole HCV polyprotein) are also disclosed in the specification.

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing the specification that a HCV NS3 serine protease is disclosed in the specification. (*see* Decl. of Amy J. Weiner, ¶¶ 5-13.)

Therefore, Applicants respectfully request withdrawal of this ground for rejection.

If the rejection is maintained, Applicants request the Examiner to provide an affidavit under 37 C.F.R. 1.104(d)(2) stating facts within the knowledge of the Examiner as to why the rejection should be maintained. Applicants reserve to right to explain or contradict the assertion with their own affidavits.

(iv) Claims 27-44 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner alleges that meanings of "NS3 domain HCV protease" or its "active truncation analogs" are not described in the specification. Applicants respectfully traverse.

Page 3, line 7 of the specification states: "Fig. 1 shows the sequence of HCV protease."

catalytic site is dependent on Ser¹¹⁶⁵ which is encompassed within the SEQ ID NO:65 protein.

Pages 6-7 of the specification describes one example of a NS3 domain protease (SEQ ID NO:1) which is shown to comprise the structure of a NS3 serine protease and, as discussed above, has been constructively reduced to practice.

Page 6 of the specification also defines the term "HCV protease" to refer to an HCV enzyme that exhibits proteolytic activity and "specifically the polypeptide encoded in the NS3 domain of the HCV genome." Examples 4 and 5 (pages 29-32) describe a specific protease activity associated with a "full length HCV protease." HCV protease is defined to be synonymous with full length NS3 domain protease.

As stated in the declaration of Dr. Weiner, one of skill in the art would understand from reviewing the specification the meaning of the term HCV NS3 domain protease. (*see* Decl. of Amy J. Weiner, ¶ 6.), Applicants submit that an ordinary artisan will understand the meaning of the term HCV NS3 domain protease from the specification, and respectfully request withdrawal of this ground for rejection.

If the rejection is maintained, Applicants request the Examiner to provide an affidavit under 37 C.F.R. 1.104(d)(2) stating facts within the knowledge of the Examiner as to why the rejection should be maintained. Applicants reserve to right to explain or contradict the assertion with their own affidavits.

F. Claim Rejections Under 35 U.S.C. § 102

Claims 27-31 and 44 are rejected under 35 U.S.C. § 102(a) as being anticipated by Reyes et al., WO 90/00597 and Choo et al. EP318216.

Specifically, the Examiner asserts that the claimed composition comprises a polynucleotide that is indistinguishable from the HCV genome and are thus anticipated by references disclosing HCV particles.

In response, Applicants amend claim 27 to specify that the claimed composition comprises "an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide, wherein said polypeptide consists essentially of an HCV NS3 domain protease." (emphasis added). Applicants submit that the claimed isolated polynucleotide, as amended, does not read on the native HCV genome. Therefore, references disclosing HCV particles do not anticipate claims 27-31 and 44 and Applicants respectfully request withdrawal of this ground for rejection.

CONCLUSION

In light of the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002010005. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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